Research Plan

On

CO-ORDINATION CHEMISTRY AND BIOLOGICAL ACTIVITY

For

Partial fulfillment of Ph. D. Degree in Chemistry

SUBMITTED BY
Mayank Pandya

SUPERVISOR
Dr. N. S. Chundawat
Assistant Professor

Department of Science
Faculty of Arts, Science and Commerce (FASC)
Mody Institute of Technology and Science (MITS)
(Deemed University under section 3 of UGC Act 1956)
Lakshmangarh, Sikar (Rajasthan – 332311) INDIA

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Introduction:

A large number of complexes has been synthesized in various laboratories throughout the world. For this purpose transition metals are found to be most suitable. A number of ligands has been synthesized and were exposed to metals for formation of complexes. These complexes were of various kind namely binary, ternary complexes etc. with presence and absence of chelate rings. It has been found in many of the cases that the biological activities of ligands are highly enhanced by participating in complex formation and this is one of the most important propellant for the studies of these metal complexes. A good amount of work has also been carried out for synthesis and isolation of mixed ligand complexes. These complexes which has been synthesized by using various ligands and metals found vast applications in many fields. The studies like spectrophotometric, potentiometric, polarographic and XRD also has been carried out for above mentioned simple and mixed-ligand complexes.

Objective:

In this proposed research work synthesis of various ligands will be carried out, which will be followed by the synthesis of transition metal complexes. Our main objective is to synthesize complexes, thenspectrophotometric studies and biological activities. The efforts will also be made to isolate the solid complexes for the characterization and biological activities. So in nutshell the proposed work will consist of synthesis of various ligands, their complexes, characterization of synthesized ligands and complexes and their biological activities.

Review of Literature:

A survey of literature has been carried out regarding spectrophotometric methods and biological activitieswhich is presented in form of review. The information has been condensed in tabular form under the following heading: Name of the reagent, λ_{max} or working wavelength with optimum pH and remarks.

S.NO.	Name of the Reagent	λ_{max}	pH	Remarks
1.	4-(2-Pyridylazo) Resorcinol (PAR)	493 nm	9.0	A new concentration online system followed by spectrophotometric determination of Zinc (II), Copper (II), lead (II) and cadmium (II) has been developed. The method is based on the absorption of metal ions on inner surface of glass capillary tubes. The metal ions that were concentrated on a glass surface for 5 minutes were eluted online with a small amount of dil.HNO_3 solution in carries time. The flow system was composed of four channels, including the carrier, sample solution, buffer solution and detection reagent. The concentration efficiencies of Zinc (II), Copper (II), lead (II) and cadmium (II) obtained by present method are 166, 143, 394 and 102 times respectively. Further, the eluted metal ions were then determined with 4-(2-Pyridylazo) Resorcinol (PAR) by spectrophotometry. The optimum condition of pH and working wavelength are 9.0 and 493 nm for zinc, 9.0 and 517 nm for copper, 8.5 and 520 nm for lead and 9.5 and 504 nm for cadmium. PAR solution of pH 10 and concentration 4.0×10^{-4} M was used in the process.

2.	Eriochrome blue black R	-	-	A new method for determination of trace zinc has been developed. Method involves the decolorizing reaction catalyzed by zinc (II) which results from the oxidation of eriochrome blue black R by hydrogen peroxide in sulphuric acid medium. The decrease in color is in proportion of zinc (II) amount. The method is highly sensitive with minimum quantity determination being $1.5x10^{-10}$ gm/ml.
3.	Phenyl Pyruvic acid thiosemicarbazone (PPVAT)	300-450 nm	8.5	A method for simultaneous determination of zinc and copper with PPVAT by second derivation spectrophotometry has been proposed. A portion of mixed solution of copper (II) and zinc (II) is treated with 5 ml of ammonia-ammonium chloride buffer of pH 8.5, 1 ml ethanolic $5x10^{-3}$ M PPVAT and the mixture obtained is subjected to absorbance measurement between 300-450 nm. A second derivative method has been proposed and used for simultaneous determination of zinc and copper in synthetic mixture.

4.	2-(5-Bromo-2-pyridylazo)-5-diethylamino phenol 2-(5-Br-PADAP)	555 nm	8.5	A method has been proposed for spectrophotometric determination of zinc in aluminum alloys. The color reaction of zinc (II) with 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol has been studied in presence of surfactant such as cetyltrimethyl ammonium bromide (CTMAB), Tween-20, Triton X-100 in the ammonium hydroxide-ammonium chloride buffer (pH=8.5). CTMAB has been found to best enhance sensitivity effect. The red complex of zinc (II) with 5-Br-PADAP has maximum absorptivity at 555 nm.
5.	Xylenol orange (XO)	500-571 nm	5.98	A method has been developed for simultaneous spectrophotometric determination of zinc and iron by multivariable calibration. It has been reported in this work that any of zinc (II) and iron (III) ions could react with xylenol orange (XO) at pH 5.98 acetic acid-sodium acetate buffer solution to form stable colorful complexes. Their absorption maxima lay at 571 nm and 500 nm and absorption spectra overlapped. The overlapped spectral data have been treated by multivariate calibration of chemo metric approaches. The linear range of the

				calibration curves for zinc and iron have been found to be 0.5-4μg ml^{-1} and 0.2-1.8 μg ml^{-1} respectively. The limit was 0.13 μg ml^{-1} for both zinc and iron. Chemo metric methods such as partial least square algorithm have been applied to the simultaneous spectrophotometric determination of zinc and iron in food samples with satisfactory results.

S.NO.	Name of compound	Biological Activity	Remarks
1	3-(4-Hydroxyphenyl)-1-(4-chlorophenyl)-2-propen-1-one 3-(4-Hydroxyphenyl)-1-(4-bromophenyl)-2-propen-1-one	Antimicrobial activityof these twocompounds has beendetermined against human pathogenic bacteria viz.*Staphylococcus aureus* and *pseudomonas aeruginos* by disc diffusion method.	These two synthesized compounds showed excellent activity. They showed 21.4 mm, 32.3 mm and 22.6 mm, 32.8 mm zone of inhibition against *Staphylococcus aureus* and *pseudomonas aeruginosa* bacteria at 500μg/ml and 1000 μg/ml concentrationrespectively.
2	2-[3'-Chlorophenyl iminomethyl] phenol	Antibacterial activity of this compound has been determined against *Eschericia coli* by cup or agar well assay method.	This compound showed 24 mm zone of inhibition against *E.coli*. This compound has marginally better activity as compared to standard drugs.

3	3-Hydroxy-3-p-tolyl-1-p-tolyltriazene 3-Hydroxy-3-p-tolyl-1-p-chlorophenyltriazene	Antibacterial activity of these compounds has been determined against *Protius mirabilis* by cup or agar well assay method.	These compounds showed 16 mm and 17 mm zone of inhibition against*Protius mirabilis*respectively. Both compoundshas better activity as compared to standard drugs.

Materials and Methods:

Almost all the chemicals which are required for the proposed work are available in our chemistry laboratory. Synthesis of ligands and complexes will be carried out with conventional methods which have already been mentioned in literature.

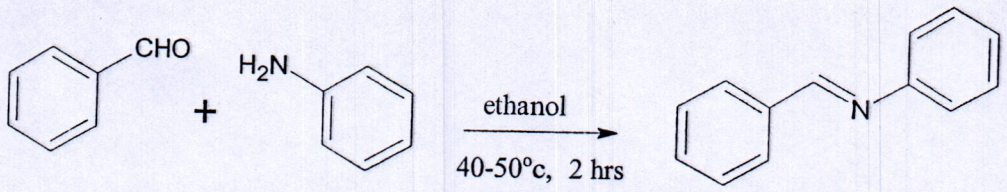
Efforts will also be made to find the new pathways for synthesis of various ligands and complexes.

The conventional methods which will be followed for some of the useful ligands is as under-

A. Synthesis of Schiff's Bases

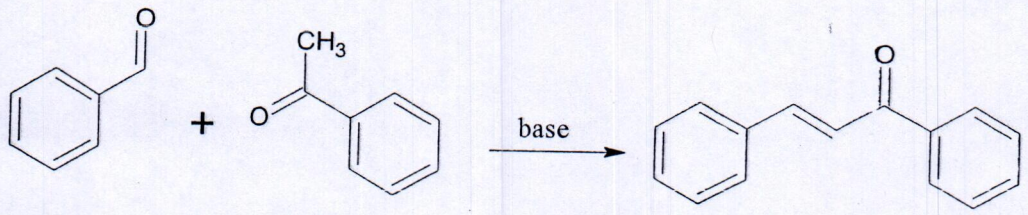
Schiff bases are condensation products of primary amines with carbonyl compounds and they were first reported by Hugo Schiff in 1864. These compounds are also known as anils, imines or azomethines.

A solution of aromatic amines (dissolved in minimum quantity of absolute ethanol) is slowly added to a solution of aromatic aldehyde derivatives (dissolved in 30 ml absolute ethanol). After stirring the reaction mixture for two hours at 40°-50°C and then subsequent coolingwhich results in precipitation. The precipitate, after filtration is followed by washing several times with cold water, then recrystallized from ethanol.



B. Synthesis of Chalcones

A mixture of aldehyde and ketone is stirred in ethanol (30 ml) and then an aqueous solution of potassium hydroxide (40%, 15 ml) is slowly added to it. The reaction mixture is allowed to stand overnight at room temperature and then it is poured in to crushed ice and acidified with dil.HCl. The solid separated is filtered and recrystallized from ethanol.



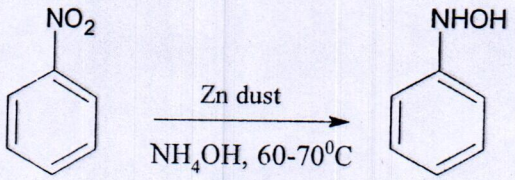
C. Synthesis of Hydroxytriazenes

Bamberger first reported this method. It has subsequently been used by Elkins and Hunter &Sogani and Bhattacharya.

This method involves three steps for synthesis of hydroxytriazene.

Step (i)

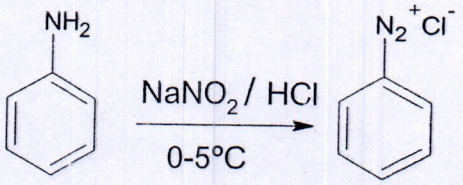
This step involves the reduction of nitrobenzene, substituted nitrobenzene or nitroalkane with zinc and ammonium hydroxide in neutral medium maintaining temperature between 60-70°C to give corresponding alkyl hydroxylamine or aryl hydroxylamine.



Phenyihydroxylamine

Step (ii)

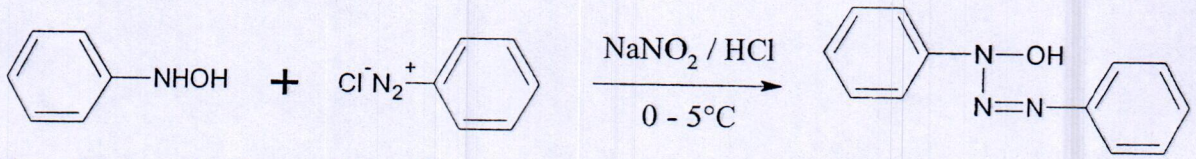
This step involves diazotization of arylamine with sodium nitrite and hydrochloric acid at temperature below 5°C to form corresponding diazonium salt.



Phenyldiazonium chloride

Step (iii)

This step involves the coupling of aryl or alkylhydroxylamine with aryldiazonium salt at temperature below 5°C in buffered medium of sodium acetate (pH = 5-6) to form hydroxytriazene.



Phenylhydroxylamine **Phenyldiazonium chloride**

The efforts will also be made to synthesis some more useful ligands for the proposed work.

General methods for synthesis of complexes:

- A Solution of synthesized ligand is kept in ice bath, which is followed by dropwise addition of metal solution along with continuous stirring. After the complete addition of the metal solution, the reaction mixture was further stirred for 10 minutes and kept in ice bath for 2 hours. The complex formed is filtered under suction and washed with double distilled water. After drying at room temperature complex formed is finally recrystallized with ethanol.
- A mixture of metal salt and ligand in ethanol is refluxed for 3 hours. The resulting mixture is concentrated to about a third of its volume and then cooled at room temperature. The precipitate that formed is filtered, washed with ethanol and dried.

Scope of the work:

Review of literature reveals that large number of complexes and ligands had been synthesized and isolated for their biological activities and it has been found that many of them showed excellent activities against number of bacteria, viruses, fungi and insects. These compounds and complexes found vast applications in anti-cancer, anti-tuberculosis, anti-inflammatory, anti-chagas activity etc. The studies of complexes show that when ligands involves in bond formation in majority of cases, the biological activities of above said ligands enhanced many times. This is also one of the reason for the studies of various complexes either binary, ternary etc. with different metals. The elegant biological activities of ligands and complexes also found vast application in field of pharmaceutical.

Facilities and Work Place:

Almost all the facilities and instruments are available in our laboratory and those which are not available like IR, NMR, and elemental(C, H,N) analyzer; these studies will be get done from institute like CDRI Luknow, SAIF and other laboratories, microbiology laboratory of M.S. University Vadodara. Whole of the work will be carried out at Mody University of Science and Technology, Faculty of arts, science and commerce, chemistry laboratory Lakshmangarh Sikar.

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